REMARKS

Claims 2 - 4, 7 - 9, 13 and 15 – 31 are pending in application, with claims 7 and 8 withdrawn from consideration as directed to non-elected subject matter. Claims 2, 3 and 17 have been amended. Accordingly, claims 2 - 4, 7 - 9, 13, and 15 – 31 will remain pending in the application upon entry of the amendments presented herein.

The claims have been amended to recite more clearly the instant invention, to make editorial changes and otherwise to expedite prosecution of the application. In particular, claim 2 has been amended to remove all occurrences of the term "prodrug"; claim 3 has been amended to correct a typographical omission; and claim 17 has been rewritten in independent form. Support for the amendments can be found throughout the specification and claims as originally filed. No new matter has been added.

Amendment and cancellation of the claims are not to be construed as acquiescence to any objections/rejections set forth in the Office Action and were made solely to expedite prosecution without prejudice to pursuing the original subject matter of this application in a later filed application claiming benefit of the instant application, including without prejudice to any determination of equivalents of the claimed subject matter.

Applicant also requests rejoinder of the withdrawn claims of commensurate scope to the provisionally elected method of prevention and/or treatment claims upon allowance of claims directed to the elected invention.

Declaration of Luciano Adorini

Applicant submits herewith the Declaration of Luciano Adorini ("Adorini Declaration"), which is referenced in the remarks below.

Supplemental Information Disclosure Statement

Applicant submits herewith a Supplemental Information Disclosure Statement.

Claim Rejections – 35 U.S.C. §112, First Paragraph – "New Matter"

Claims 2 - 4 and 9, 13 and 15 -31 are rejected under 35 U.S.C. §112, first paragraph, failing to comply with the written description requirement. In particular, the Office Action sets forth the allegation that the disclaimer in claim 2 is considered "new matter". Applicants respectfully disagree and traverse the rejection.

Applicant contends that the proviso (disclaimer) recited in claim 2 does not introduce new matter. *See, In re Johnson*, 194 U.S.P.Q. 187 (C.C.P.A. 1977).

In *In re Johnson*, the Requester/Patentee amended its generic claim to *exclude* certain species (or subgenuses) disclosed in a patent of another. In reversing the USPTO's rejection of those amended claims for allegedly lacking adequate written description, the Court stated:

> The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and thus has failed to satisfy the requirements of §112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute. . . . [T]he "written description" in the [parent application] specification supported the claims in the absence of the limitation, and that specification, having described the whole, necessarily described the part remaining. . . . **[U]nder these circumstances . . . appellants are merely excising the invention of another, to which they are not entitled, and are not creating an "artificial subgenus" or claiming "new matter."** [Emphasis added.]

In re Johnson, 194 U.S.P.Q. at 196.

In the present application, the amendment made to claim 2 excises two subgeneric formulae of Vitamin D_3 compounds, which are alternative embodiments that are positively recited in the specification at pages 21 and 27, from the generic

class of Vitamin D_3 compounds, and does not create an artificial subgenus or add new matter.

In the first bulleted point on page 4, the Office Action cites M.P.E.P. §2173.05 and *In re Johnson*, indicating that any negative limitation or exclusionary proviso must have basis in the original disclosure and that only if alternative elements are positively recited in the specification, the such alternative elements may be explicitly excluded from the claims. The Office Action goes on to allege that the proviso does not have basis in the original disclosure and that the alternative elements recited in the proviso of claim 2 are generic structures and, as such, are not positively recited in the specification. Applicant respectfully disagrees.

Neither the M.P.E.P. nor *In re Johnson* requires that there be literal support for a proviso in the specification. Rather, support for a proviso in the disclosure exists as long as the proviso does not create an "artificial subgenus" or claim "new matter." *See*, *In re Johnson*, 194 U.S.P.Q. at 196.

In this case, Applicant has not created an artificial subgenus nor claimed new subject matter. Applicant has disclosed and claimed a broad aspect of the invention, namely, methods for treating overactive bladder ("OAB"), using a vitamin D_3 compound. (Specification, page 6, lines 11-13 and 31-33; and page 12, line 31 through page 13, line 5.)

The invention is described as including the use of a plurality of alternative compound embodiments, described as subgeneric formulae and specific compounds. In this regard, the Examiner is invited to note the use throughout pages 16 – 40 of the phrases "in one embodiment..., in another embodiment..., in yet another embodiment..., in a further embodiment..., etc.". Thus, the invention includes and, therefore, contemplates the possibility of excluding one or more of the disclosed embodiments because the disclosed embodiments are positively recited in the alternative.

In particular, the specification describes a plurality of alternative compounds embodiments in terms of various subgenuses of vitamin D compounds and vitamin D_3 compounds, subgeneric formulae of various families of vitamin D_3 compounds and

specific compounds within those families. In this regard, Applicant invites the Examiner's attention to pages 16 – 40 of the specification where a plurality of alternate embodiments are clearly and positively described

In particular, the two generic formulae excluded from the scope of claim 2 are positively recited in the specification at page 24, lines 1-21 and page 27, lines 6-18, respectively, as alternative embodiments/elements of the invention. Thus, exclusion of one or both of these two generic formulae does not create an artificial subgenus as subgenuses excluding one or the other of the generic formulae were clearly contemplated.

The Office Action sets forth the position that because the elements excluded from claim 2 are generic structures, they are not positively recited. As shown above, that is certainly not the case. Moreover, the Court in *In re Johnson* made no statements that could be construed to prohibit the exclusion of generic formulae from a claim.

The Court stated that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has not failed to disclose and teach those skilled in the art how to make and use that genus minus two of those species. Likewise, Applicant has fully disclosed and taught those skilled in the art how to make a use a genus of compounds and numerous subgeneric compounds and species therewithin (in the instant application, subgenuses and specific compounds falling within the genus and subgenuses) and, therefore, has not failed to disclose and teach those skilled in the art how to make and use that genus, minus two subgenuses that are positively described in the alternative.

Indeed, the facts as presented herein are clearly in conformity with those presented in *In re Johnson*. In fact, the situation here is the very situation that the Court in *In re Johnson* sought to address and prohibit; namely, "a hypertechnical application of legalistic prose relating to that provision of the statute [35 U.S.C. §112, first paragraph]..."

In the first bullet on page 5, the Office Action indicates that '[i]n the present case compounds were generically disclosed. After the rejection Applicants have disclaimed

the specific compounds which were taught by the prior art." This statement is not correct.

Applicant respectfully invites the Examiner's attention to the fact that there is no mention whatsoever in claim 2 of the prior art compounds. Applicant did not disclaim the specific compounds taught in the prior art but rather disclaimed two genuses of compounds positively and alternatively disclosed in the application. Because the prior art compounds fall within the excluded genuses, they are *de fac*to excluded from claim 2. This is permitted by the holding of the Court in *In re Johnson* because the excluded elements (the two subgenuses in question) are positively and alternatively disclosed in the application. Applicant, like Johnson, is "doing nothing more that excising the invention of another, to which [he is] not entitled, and [is] not creating an 'artificial subgenus' or claiming 'new matter' ".

In the remaining bullets on page 5 and 6, the Office Action includes citations to other cases. However, these cases are distinguishable on their facts from the facts of *In re Johnson* and those of the instant application.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection for lack of written description under 35 U.S.C. §112, first paragraph.

Claim Rejections -35 U.S.C. § 112, First Paragraph – "Written Description"

Claims 2 - 4 and 9, 13 and 15 -31 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. It is alleged that "[t]here is no teaching or guidance how 'prevention' and 'treatment' of ***bladder dysfunction*** by such a large number of compounds would be treated successfully." Applicant respectfully disagrees and traverses the rejection.

The term "bladder dysfunction" is highlighted in the paragraph above because the Examiner apparently failed to consider that in the response filed June 9, 2008 to the previous Office Action, Applicant significantly narrowed the scope of claim 2 by amending it to recite "***overactive bladder***" as the type of bladder dysfunction and

"***Vitamin D_3***" compounds as a subclass of Vitamin D compounds. Applicant respectfully requests that the Examiner acknowledge that the scope of the claims has been narrowed as described above. Applicant also notes that in the section titled "Response to Remarks" on pages 16-17 of the instant Office Action, the Examiner did not address Applicant's arguments made at pages 14-15 of Applicant's response filed on June 9, 2008.

Accordingly, Applicant traverses the rejection for the reasons of record as set forth in the June 9, 2008 response and reiterates those arguments here.

Regarding the term "preventing," Applicant notes that the M.P.E.P. (8th edition, Revision No. 6) states at section 2163.02, that written description can be demonstrated by the following:

> the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention...Possession may be shown in a variety of ways including description of an actual reduction to practice...

Applicant submits that working Examples 47 (pages 120-123) and 51 (pages 127-130) of the application as filed provide adequate written description that is commensurate in scope with the claims presented herein for preventing or treating overactive bladder.

Example 47 demonstrates the activity of calcitriol and a number of Vitamin D_3 analogs (see the table on pages 120-122) on the growth and function of bladder cells. Specifically, Applicant used an *in vitro* model of culturing human stromal bladder cells to prove that calcitriol and Vitamin D_3 have an effect on the growth and function of bladder cells.

Likewise, Example 51 describes a validated bladder outlet obstruction model that was used to evaluate the ability of vitamin D_3 analogs to control and treat bladder dysfunction. In particular, Compound A of Example 47 (1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol, recited in claim 19, which depends from claim 17) was evaluated to determine whether the compound at a dose of 150

µg/kg/daily can prevent bladder hypertrophy and bladder dysfunction such as bladder overactivity.

As shown in Example 51, Compound A had a beneficial effect on bladder function:

> "This effect was evident in the normal bladder and is maintained in bladder outlet obstruction. In particular significant differences versus vehicle were observed in:
> -spontaneous non-voiding contraction frequency and amplitude (Figures 15 and 16);
> -residual urine (absent with the active compound, Figure 20);
> -micturition pressure (Figure 19).
> In addition a beneficial effect on bladder function has been confirmed in the *in vitro* tests:
> -K response;
> -response to EFS (Figure 21);
> -response to carbachol.
> Finally a slight decrease in bladder weight was observed with the vitamin D_3 analogue tested (Figure 16).
> These data demonstrate the use of vitamin D analogues (in the dose range from 50 µg to 300 µg - equivalent to approximately 0.725 to 5 µg/kg of body mass in humans) in the ***prevention and treatment of bladder dysfunction, such as overactive bladder***." [Example 51, page 130, lines 1-19. Emphasis added.]

Applicant respectfully submits that the specification, particularly when read in light of Examples 47 and 51, conveys with reasonable clarity to those skilled in the art that, as of the filing date of the application, Applicant was in possession of methods for preventing and treating ***overactive bladder*** by administering a ***Vitamin D_3 compound***, as recited in the claims presented therein. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph – "Indefiniteness"

Claims 2 and 3 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, it is alleged that there are no steps for obtaining or synthesizing a vitamin D compounds and the claims are open ended. Applicant respectfully disagrees and traverses the rejection for the reasons set forth in the response filed June 9, 2008 and reiterates those reasons here. (As a preliminary matter, Applicant does not understand why claim 2 is rejected because claim 2 does not recite the step of obtaining or synthesizing. Accordingly, the rejection of claim 2 should be withdrawn as it is improper.)

As presented herein claim 3 is directed to the method of claim 2, "which further comprises the step of obtaining or synthesizing the Vitamin D_3 compound." This claim was drafted specifically for the purpose of optimizing enforcement of the patent. In other words, the person who practices the method of claim 2 must obtain the Vitamin D_3 compound or synthesize it in order to practice the method. If the person obtains the compound, he/she must purchase it or otherwise acquire it from a third party. In providing the compound to the person who practices the claimed method, the third party is inducing infringement. The acts of obtaining (purchasing or otherwise acquiring) and synthesizing are activities that are easily traced, thereby facilitating enforcement of the claims.

One of ordinary skill in the art will readily appreciate the meaning of "obtaining" in this context. Furthermore, the application describes on pages 49-52 and in working Examples 1-46 the syntheses of the vitamin D_3 compounds of the invention. Pages 49-52 of the application also provide numerous literature references and published patents and patent applications describing the syntheses of various compounds of the invention, and those references have been incorporated into the application by reference. Applicant submits that claim 3 is sufficiently definite within the meaning of the second paragraph of 35 U.S.C. §112 and, therefore, respectfully requests reconsideration and withdrawal of the rejection.

Double Patenting Rejection

Claims 2 - 4 and 9, 13 and 15 -31 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting over claims 1 - 6, 8, 9, 11, 12, 15, 23, 24, 31 and 32 of application Ser. No. 10/903,211 (now U.S. Patent 7,332,482, the "482 patent"). (In view of the issuance of U.S. Patent 7,332,482, Applicant assumes that the obviousness-type double patenting rejection is no longer provisional.) It is alleged that the claims of the '482 patent are drawn to methods of treating benign prostatic hyperplasia (BPH) using 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol and, therefore, the claims of the '482 patent and the claims of the application, drawn to preventing or treating bladder dysfunction, are not patentably distinct. Applicant respectfully disagrees and traverses the rejection for the reasons of record set forth in the response filed on June 9, 2008 and reiterates those reasons here by reference.

Applicant will further address the obviousness-type double patenting rejection upon a finding that the claims are in condition for allowance but for the obviousness-type double patenting rejection.

Claim Rejections - Rejection under 35 U.S.C. § 103 – 1st Rejection

Claims 2 - 4 and 9, 13 and 15 – 31 are rejected under 35 U.S.C. § 103 as being unpatentable over Batcho (US 5,939,408), Bishop, *et al.* WO 98/29123 ("Bishop I") and Bishop, *et al.* US 6,566,353 ("Bishop II"). It is alleged that Batcho, Bishop I and Bishop II teach the use of a vitamin D compound to treat BPH. Specifically, it is alleged that Batcho teaches the use of 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol to treat neoplastic disease, Bishop I teaches methods of treating prostatic disease, including prostate cancer and prostate hyperplasia, using vitamin D compounds, and Bishop II teaches methods of treating hypercalcemia using a vitamin D compound. It is then alleged that it would have been obvious to one of ordinary skill in the art to use 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol to treat prostate hyperplasia and, hence bladder dysfunction, upon a

reading of all three references in combination. Applicant respectfully disagrees and traverses the rejection.

As noted above, the claims were amended in Applicant's response filed on June 9, 2008 and are directed to a method for preventing or treating ***overactive bladder*** using Vitamin D_3 compounds. However, it appears from the rejection that the Examiner is reading the claims as if still directed to bladder dysfunction and has overlooked that the claims are now directed to ***overactive bladder***.

For a rejection under 35 U.S.C. § 103 to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). There must also be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification."

Batcho teaches the synthesis of various vitamin D compounds and the use of such compounds in treating hyperproliferative skin diseases or neoplastic disease. Batcho does not provide any teaching or suggestion to treat overactive bladder. (Adorini Declaration, para. 7)

Moreover, hyperproliferative skin diseases and neoplastic disease, and the underlying causes of such diseases, are characterized by abnormal cell proliferation and, therefore, are so distinct from overactive bladder, a muscular dysfunction, and its underlying causes that one of ordinary skill in the art would not be motivated, based on the teachings of Batcho, to use the compounds disclosed in Batcho to treat overactive bladder.

Bishop I teaches the use of various vitamin D compounds to treat prostatic disorders such as prostate cancer and prostatic hyperplasia. Bishop I does not

provide any teaching or suggestion to treat overactive bladder. (Adorini Declaration, para. 7)

By definition, prostatic disorders such as prostate cancer and prostatic hyperplasia are necessarily related to the prostate gland and are characterized by abnormal cell proliferation that causes an enlarged prostate gland (hence a disorder that affects only men), which can cause problems of urinating due to squeezing or partial blocking of the urethra. (Adorini Declaration, para. 8)

In contrast, overactive bladder is a disorder characterized by dysfunction of the bladder detrusor muscle and, therefore, affects men and women. The urinating problems associated with overactive bladder, which include urinary urgency, frequency and nocturia, are caused by repeated and uncontrolled contractions of the bladder detrusor muscle. (Adorini Declaration, para. 10)

However, notwithstanding the similarity in lower uninary tract symptoms, one of ordinary skill in the art would not consider treatment of overactive bladder to be obvious in view of treatment of prostate cancer and prostatic hyperplasia because the underlying causes (*i.e.*, enlarged prostate gland for prostate cancer and prostatic hyperplasia and repeated and uncontrolled bladder contractions for overactive bladder) and associated mechanisms are distinct and because prostate cancer and prostatic hyperplasia only affect men whereas overactive bladder affects both men and women. (Adorini Declaration, para. 11)

Moreover, Bishop I is largely directed to the treatment of cancer. In contrast, the claims of the application are not directed to cancer treatment (see page 6 of the application, line 33).

Bishop II discloses a method of treating hypercalcemia associated with malignant or neoplastic cells by treating the cells with a Vitamin D compound where the cells are bladder cancer cells. However, Bishop II neither teaches nor suggest treating overactive bladder. (Adorini Declaration, para. 7) Moreover, the types of bladder dysfunction contemplated by the invention, such as overactive bladder, exclude bladder cancer (see page 6 of the application, line 33).

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Batcho, Bishop I and Bishop II, whether alone or in combination, do not disclose "overactive bladder," and further do not teach or suggest that vitamin D3 compounds can be used to prevent or treat overactive bladder. (Adorini Declaration, para. 7) Thus, even if there were some motivation to combine the references, the combination does not provide all of elements of the Applicant's claims as presented herein.

Even if, *arguendo*, all of the elements of the claimed invention were considered to be present in some combination of the cited prior art, there does not exist any motivation to combine there references in the first instance, nor does there exist any reasonable expectation of success that the claimed invention could be carried out by their combination. Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure. *In re Dow Chemical*, 5 U.S.P.Q. 2d 1531 (Fed. Cir. 1988).

There is nothing in either of Batcho, Bishop I or Bishop II that would motivate one of ordinary skill in the art to modify the teachings of the references or to combine the references to arrive at the invention as claimed herein. There is no teaching or suggestion in any of the references that hyperproliferative skin diseases/neoplastic disease and prostatic disorders are somehow equivalent or interchangeable such that a treatment for hyperproliferative skin diseases/neoplastic disease would be an effective treatment for prostatic disorders.

Moreover, even if there were some motivation to combine the references, the combination would not provide all of elements of the Applicant's claims as presented herein because neither reference teaches or suggests treatment of overactive bladder. (Adorini Declaration, para. 7) As noted above, hyperproliferative skin diseases/neoplastic disease, prostatic disorders and overactive bladder are distinctly different diseases. (Adorini Declaration, paras. 8 -11) Applicant submits that one of ordinary skill in the art would consider them as distinct and not interchangeable.

Given the vast differences between cell proliferation disorders (*e.g.*, prostate cancer, prostatic hyperplasia, hyperproliferative skin diseases and neoplastic disease) and muscle contractile dysfunction disorders (*e.g.*, overactive bladder), one of ordinary skill in the art would have no motivation whatsoever to modify the teachings of the cited art in the manner suggested in the Office Action, much less any reasonable expectation of success in preventing or treating overactive bladder. (Adorini Declaration, para. 12)

Applicant further submits that reliance on the KSR decision as set forth on page 13 of the Office Action is misplaced. The KSR decision was issued over 2 years ago and its holding has been limited largely to inventions falling within the "predictable arts".

One of the more recent Federal Circuit decisions addressing the use of the teaching, suggestion, motivation test post-KSR is *Ortho-McNeil Pharmaceutical v. Mylan Labs* (Fed. Cir. 2008). The Court indicated that the KSR decision, which arguably limited reliance on the teaching, suggestion, motivation test, is applicable to a limited set of circumstances in which the ***art is predictable*** and there are ***a finite number of options***. The Federal Circuit reasoned that *KSR* relates to the situation where a *finite, and in the context of the art, small or easily traversed, number of options* that would convince an ordinarily skilled artisan of obviousness and that the teaching, suggestion, motivation test remains "the primary guarantor against a non-statutory hindsight analysis."

One of ordinary skill in the art would hardly characterize the biochemistry associated with vitamin D therapies as "predictable".

To properly determine a *prima facie* case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." *Id.*

Applicant submits that the instant rejection is nothing more than a hindsight reconstruction of the claimed invention ***based on Applicant's own teachings***.

Although an Examiner often uses hindsight in formulating an obviousness rejection, such use of hindsight is permitted as long as the legal conclusion is ***gleaned from the prior art and not from Applicant's teachings***.

In this case, the rejection is the product of an improper hindsight analysis of the claims because one of ordinary skill in the art would have had no motivation to combine the references in the way the Office Action has described. Moreover, even if some motivation to combine the references did exist, one of ordinary skill in the art would have no reasonable expectation of success in practicing the claimed invention based on the teachings of the cited references, taken alone or in any combination. Accordingly, the only way the rejection could have been made is based on Applicant's own teachings.

Applicant submits that the Office Action fails to make out a *prima facie* showing of obviousness and that the claims presented herein are patentable under 35 U.S.C. § 103 over Batcho, Bishop I and Bishop II and respectfully requests reconsideration and withdrawal of the rejection.

Claim Rejections - Rejection under 35 U.S.C. § 103 – 2nd Rejection

Claims 2-4, 9, 13 and 15-31 are rejected under 35 U.S.C. § 103 as being unpatentable over Batcho (US 5,939,408), in view of Crescioli (J. Clinical Endocrinology & Metabolism). It is alleged that Batcho teaches 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol and its use to treat neoplastic disease. It is alleged that Crescioli teaches a vitamin D compound to treat BPH. It is then alleged that it would have been obvious to one of ordinary skill in the art to select the compound of Batcho to use in the method of treating BPH as disclosed in Crescioli. Applicant respectfully disagrees and traverses the rejection.

Claim 2 has been amended to recite a method of preventing or treating ***overactive bladder*** using a Vitamin D_3 compound. In contrast, Batcho teaches the synthesis of various vitamin D compounds and the use of such compounds in treating hyperproliferative skin diseases or neoplastic disease. Batcho does not provide any

teaching or suggestion to treat bladder dysfunction, and clearly does not teach or suggest the prevention or treatment of overactive bladder. (Adorini Declaration, para. 7)

Moreover, hyperproliferative skin diseases and neoplastic disease, and the underlying causes of such diseases, are characterized by abnormal cell proliferation and, therefore, are so distinct from overactive bladder, a muscular dysfunction, and its underlying causes that one of ordinary skill in the art would not be motivated, based on the teachings of Batcho, to use the compounds disclosed in Batcho to treat overactive bladder. (Adorini Declaration, para. 8)

Crescioli teaches that 1,25-dihydroxy-16-ene-23-yne D3 affected BPH cell proliferation and counteracted the activity of certain growth factors of BPH cells. The investigators then conclude that 1,25-dihydroxy-16-ene-23-yne D3 would be effective in treating BPH. Crescioli neither teaches nor suggests treatment of overactive bladder. (Adorini Declaration, para. 7)

BPH (benign prostatic hypertrophy) is characterized by an enlarged prostate gland (hence a disorder that affects only men), which can cause mild to moderate problems of urinating due to squeezing or partial blocking of the urethra. (Adorini Declaration, para. 9)

In contrast, overactive bladder is a disorder characterized by dysfunction of the bladder detrusor muscle and, therefore, affects men and women. The urinating problems associated with overactive bladder, which include urinary urgency, frequency and nocturia, are caused by repeated and uncontrolled bladder contractions. (Adorini Declaration, para. 10)

Although the symptoms of both disorders relate to urinating problems, one of ordinary skill in the art would not consider treatment of overactive bladder to be obvious in view of BPH because the underlying causes (*i.e.*, enlarged prostate gland for BPH and repeated and uncontrolled bladder contractions for overactive bladder) are distinct and because BPH only affects men whereas overactive bladder affects both men and women. (Adorini Declaration, para. 11)

Furthermore, one of ordinary skill in the art would consider BPH and overactive bladder as distinctly different diseases involving different target cells and different mechanisms. One of ordinary skill in the art would view BPH as an inflammatory disease and overactive bladder as a muscular dysfunction. (Adorini Declaration, para. 11) As such, one of ordinary skill in the art would have no reasonable expectation of success of using a vitamin D3 compound to treat overactive bladder based on the teachings of Crescioli. (Adorini Declaration, para. 12)

There is nothing in either Batcho or Crescioli that would motivate one of ordinary skill in the art to modify the teachings of the references or to combine the references to arrive at the invention as claimed herein. There is no teaching or suggestion in either reference that hyperproliferative skin diseases/neoplastic disease and BPH are somehow equivalent or interchangeable such that a treatment for hyperproliferative skin diseases/neoplastic disease would be an effective treatment for BPH.

Moreover, even if there were some motivation to combine the references, the combination would not provide all of elements of the Applicant's claims as presented herein because neither reference teaches or suggests treatment of overactive bladder. (Adorini Declaration, para. 7) As noted above, hyperproliferative skin diseases/neoplastic disease, BPH and overactive bladder are distinctly different diseases and would considered as such by those of ordinary skill in the art. (Adorini Declaration, paras. 9, 10 and 11)

Again, the rejection is the product of an improper hindsight analysis of the claims because one of ordinary skill in the art would have had no motivation to combine the references in the way the Office Action has described. Moreover, even if some motivation to combine the references did exist, one of ordinary skill in the art would have no reasonable expectation of success in practicing the claimed invention based on the teachings of the cited references, taken alone or in any combination. Accordingly, the only way the rejection could have been made is based on Applicant's own teachings.

Applicant submits that the Office Action fails to make out a *prima facie* showing of obviousness and that the claims presented herein are patentable under 35 U.S.C. §

103 over Batcho and Crescioli and respectfully requests reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully request favorable reconsideration and withdrawal of all rejections, and allowance of this application with claims 2 - 4, 7 - 9, 13 and 15 - 31 presented herein. If a telephone conversation with Applicant's representative would help expedite the prosecution of the application, Applicant urges the Examiner to call the undersigned at (617) 517-5509.

Applicant authorizes the Director to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 04-1105, under Order No. 62138US(49949).

Respectfully submitted,

Dated: August 10, 2009

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